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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/596,101 | 06/16/2000 | Patrick de Baetselier | 4432US | 2709 |

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| EXAMINER | |
|---|---|
| FORD, VANESSA L | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1645 | |

DATE MAILED: 11/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/596,101 | Applicant(s) DE BAETSELIER ET AL. | |
|---|---|---|---|
| | Examiner Vanessa L. Ford | Art Unit 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *21 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *4-10,12,14,15,18 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,11,13, 16,17 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 June 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 21, 2003 has been entered. Applicant's amendment is acknowledged. Claims 1-3, 11, 13 and 16-17 have been amended. Claim 20 has been added.

### *Rejections Maintained*

2. The rejection of claims 1-3, 13 and newly submitted claim 20 under 35 U.S.C. 102(b) as anticipated by Bilej et al *(European Cytokine Network, March-April 1994)* is maintained for the reasons set forth on pages 2-4 of the previous Office Action.

The rejection was on the grounds that Bilej et al teach a coelomic fluid from the *Eisenia foetida* earthworm that exerts a strong trypanolytic activity. Bilej et al teach that the coelomic fluid of the earthworm contains strong proteolytic, hemolytic, bacteriolytic and cytolytic factors and may be an ancestral form of TNF-$\alpha$. It would be inherent that the CCF-1 protein as taught by Bilej et al would comprise at least 9 contiguous amino acids of SEQ ID No: 1 or comprise the amino acid sequence of SEQ ID NO: 3 or a functional fragment thereof.

Since the Office does not have the facilities for examining and comparing applicant's polypeptide with the polypeptide of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the polypeptide of the prior art does not possess the same material structural and functional characteristics of the claimed polypeptide). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant urges that claims 1 and 2 are not anticipated by Bilej et al since Bilej et al do not disclose the isolated peptides of claim 1 or claimed 2. Applicant urges that Bilej et al teach a semi-pure active fraction of coelomic fluid.

Applicant's arguments filed August 21, 2003 have been fully considered but they are not persuasive. It is the Examiner's position that there is nothing on the record to show why the coelomic fluid from *Eisenia foetida* earthworm of the prior reference is not the same as the claimed peptide from *Eisenia foetida* earthworm. The claims are direct to isolated peptides comprising at least 9 contiguous amino acids of SEQ ID NO:1 exhibiting trypanolytic activity and an isolated peptide comprising the amino acid sequence of SEQ ID NO:3 or a functional fragment thereof having trypanolytic activity. Applicant has provided no side-by-side comparison to show: that the peptide (i.e. coelomic fluid with trypanolytic activity) of the prior art is not the same as the claimed peptide. Applicant has not defined the term "isolated" in the instant specification. Therefore, since the coelomic fluid comprising the peptide with trypanolytic activity of Bilej et al has been purified from the *Eisenia foetida* earthworm, the peptide of the prior art meets the limitations of the claimed invention.

3. The rejection of claims 11 and 16-17 under 35 U.S.C. 102(b) as anticipated by Bilej et al *(Immunology Letters, 45, 1995)* is maintained for the reasons set forth on, pages 4-6 of the previous Office Action.

The rejection was on the grounds that Bilej et al teach a concentrated coelomic fluid composition for intra-foot pad immunization of Balb/c mice (see page 124). The composition of Bilej et al is the same as the claimed invention. It would be inherent that the concentrated coelomic fluid sample would contain a peptide comprising at least 9

contiguous amino acids of SEQ ID NO: 1 or a peptide comprising the amino acid sequence of SEQ ID NO: 3 or a fragment/epitope of either thereof.

Since the Office does not have the facilities for examining and comparing applicant's pharmaceutical composition with the pharmaceutical composition of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the pharmaceutical composition of the prior art does not possess the same material structural and functional characteristics of the claimed pharmaceutical composition). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant urges that the teaching of Bilej et al do not disclose all of the elements of claim 11. Applicant urges that Bilej et al do not disclose a pharmaceutical composition that includes an isolated peptide. Applicant urges that Bilej et al teach a semi-pure active fraction of coelomic fluid.

The claims are direct to isolated peptides comprising at least 9 contiguous amino acids of SEQ ID NO:1 exhibiting trypanolytic activity and an isolated peptide comprising the amino acid sequence of SEQ ID NO:3 or a functional fragment thereof having trypanolytic activity. Applicant has provided no side-by-side comparison to show: that the peptide (i.e. coelomic fluid with trypanolytic activity) of the prior art is not the same as the claimed peptide. Applicant has not defined the term "isolated" in the instant specification. Therefore, since the coelomic fluid comprising the peptide with trypanolytic activity of Bilej has been purified from the *Eisenia foetida* earthworm, the peptide and composition of the prior art meets the limitations of the claimed invention.

***New Grounds of R jection***

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1 and 3 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. *This is a written description rejection.*

The specification broadly describes as a part of the invention an isolated peptide comprising at least 9 contiguous amino acids of SEQ ID No: 1. The specification states that "the term fragment of a sequence or part of a sequence means a truncated sequence of the original sequence referred to and that protein sequence can vary widely in length, the minimum size being a sequence of sufficient size to provide a sequence with at least a comparable function and/or activity of the original sequence referred to while the maximum size is not critical" (pages 10-11). The specification states that 'the typically the truncated amino acid sequence will range from about 5 to about 60 amino acids in length (page 11). Applicant has broadly described the invention as embracing any substitution, insertion or deletion change of amino acids throughout the length of the polypeptide sequence. Variants of SEQ ID No:1 correspond to sequences from other species, mutated sequences, allelic variants, splice variants, sequences that have a variant degree of identity (similarity, homology), and so forth.

None of these sequences meet the written description provision of 35 U.S.C. 112, first, paragraph. The specification broadly describes a genus of isolated peptides that have no structural description accompanying the variant language (i.e. comprising at least 9 contiguous amino acids) recited in the claims. While mutagenesis techniques are known in the art, it is not routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the amino acid's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining a certain activity or function are limited in any peptide and the result of such modifications is unpredictable based on the instant disclosure. Therefore, only SEQ ID NO: 1 and not the full breadth of the claim (i.e. an isolated peptide comprising at least 9 contiguous amino acids of SEQ ID NO:1) meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant.

The specification provides insufficient written description to support the genus encompassed by the claim. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NO:1, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptide regardless of the

complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Therefore, only SEQ ID NO: 1 but not the full breadth of the claim (or none of the sequences encompassed by the claim) meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

5. Claims 1-3, 11, 13, 16-17 and claim 20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification is enabling only for the peptides of SEQ ID NO:1 and SEQ ID NO:3 and which actually have trypanolytic activity, as disclosed in the specification.

The specification states "that SEQ ID NO:1 comprising 13 amino acids shows essential cytolytic, trypanolytic and glucan-binding characteristics comparable to the

whole protein" (page 10). The specification further states " that the peptide termed CCF-1/TIP (represented by SEQ ID NO:1, the trypanolytic domain) was tested in a trypanolytic assay and was found to be trypanolytic in a time and dose-dependent way" (page 17 and Figure 1). The specification does not disclose whether or not SEQ ID NO:3 or fragments or epitopes thereof have cytolytic or trypanolytic activity.

There is no guidance provided as to which amino acids can be deleted and the polypeptide would retain its biological function. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of the polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar activity/utility requires a knowledge with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the polypeptide's structure relates to function. However, the problem of the prediction of polypeptide structure from mere sequence data of a single polypeptide and in turn utilizing predicted structural determinations to ascertain functional aspects of the polypeptide and finally what changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation. There is no guidance as to what amino acids may not be changed without causing a detrimental effect to the polypeptide being claimed. The claims broadly teach polypeptides which include

substitutions and/or deletions, therefore any polypeptide is being claimed, and no specific location for the deletion, substitution or any combination thereof is recited. Thus, the resulting polypeptide could result in a polypeptide not taught nor enabled by the specification.

Thomas E. Creighton, in his book, "Proteins: Structures and Molecular Properties, 1984", (pages 314-315) teaches that variation of the primary structure of a protein can result in an instable molecule. He teaches that a single amino acid change can cause a mutant hemoglobin to have lower stabilities due to any of several causes: 1) alteration of close-packing of the interior; loss of one group that normally participates in a hydrogen bond or salt bridge; 2) the introduction of a charged or polar group into the interior or the insertion into a helical region of a Praline residue, which must distort the alpha-helix; 3) while sometimes radical changes of surface groups, even introduction of a non-polar side chain- have no great effect on stability.

Thomas E. Creighton, in his book "Protein Structure: A Practical Approach, 1989; pages 184-186" teaches that present day site directed mutagenesis of a gene allows any amino acids in a protein sequence to be changed to any other, as well as introducing deletions and insertions". The reference goes on to teach that it is difficult to know which amino acid to change and which is the best residue to substitute for the desired functional and structural effect.

Nosoh, Y. et al in "Protein Stability and Stabilization through Protein Engineering, 1991" (chapter 7, page 197, second paragraph) adds support to Thomas E. Creighton, by teaching that results so far accumulated on the stability and stabilization of proteins

appear to indicate that the strategy for stabilizing proteins differ from protein to protein and that any generalized mechanisms for protein stability have not yet been presented.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Therefore the specification fails to provide guidance regarding as to whether the peptides comprising fragments or epitopes of SEQ ID NO:1 or SEQ ID NO:3 that have cytolytic or trypanolytic activity. One of skill in the art would require guidance, in order to make or use fragments or epitopes of SEQ ID NO:1 or SEQ ID NO:3 in a manner reasonable in correlation with the scope of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting fragments or epitopes having claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make or use polypeptides that are fragments or epitopes of SEQ ID NO: 1 or SEQ ID NO:3 in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 2 is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 2 recites "functional fragment". It is unclear as to what Applicant is referring? Clarification is required.

***Status of Claims***

7. No claim allowed.

8. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Patent Examiner
November 7, 2003

MARK NAVARRO
PRIMARY EXAMINER